Simultaneous Vaccination of Adults

Armed Forces Epidemiological Board

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Issue: Is there a threshold above which giving simultaneous vaccinations to an adult in a short period of time is less safe than individual vaccinations as isolated events?

- Simultaneity more at issue than Multiplicity
  - not an issue of lifetime cumulative stimuli

- Motivations (Domains):
  - DISCOMFORT: Avoid pin-cushion effect (sore arms, etc).
  - ALLERGY: Every vaccination is a chance for anaphylaxis.
  - AUTOIMMUNE ISSUES: Address concerns about harm from simultaneity immunizations (rare events).
    - e.g., “overloading the immune system,” autoimmune disorders, death.
  - IMMUNOGENICITY: Possibility of interference between antigens.

Everyday Life

- Just a normal summer picnic:
  - Bacteria in unrefrigerated potato salad
  - Skin abrasions sliding into second base
  - High-fives after game
  - Sneezes from summer “colds” or allergies
  - Water swallowed from the pond
  - Didn’t wash hands after using outhouse
  - Bee sting
  - Ragweed pollen in the air
  - Poison ivy in the outfield
  - Later that night, unprotected intercourse

- The body is built to function normally while cruising through a landscape of multiple antigens.

Combined Immunogens are Common

Diphtheria-tetanus (DT)*1949*

Diphtheria-tetanus-pertussis (DTaP)*1949*

DTaP—Hep B—IPV (*Pediarix*, GSK)

DTaP—Hib (*TriHibit,* AvP)

Hib—Hep B (*Comvax*, Merck)

Hep A—Hep B (*Twinrix*, GSK)

Influenza A&B trivalent *1945*

Measles—Mumps—Rubella

Meningococcal polysaccharide A-C-Y-W135

Pneumococcal 7-valent conjugate (*Prevnar*, Wyeth)

Pneumococcal 23-valent polysaccharide (*Pneumovax*, Merck)

Poliovirus inactivated trivalent (*Ipol*, AvP)

Tetanus—diphtheria (Td) toxoids *1955*

Immunogens per Vaccine, Adult

adapted from Offit et al, 2002 **Vaccine** *(some values overestimate # of stimuli)*	**# of Presumptive Immunogens**
Anthrax	2
Hepatitis A	1
Hepatitis B	1
Hepatitis A—Hepatitis B	2
Influenza A&B trivalent	Jab 1*3=3 *FluMist* 9*3=27
Japanese encephalitis	10
Measles—Mumps—Rubella	10 + 9 + 5 = 24
Meningococcal A/C/Y/W-135 *polysaccharide*	4
Pneumococcal 23-valent *polysaccharide*	23
Poliovirus inactivated trivalent	15
Rabies	5
Smallpox (vaccinia)	198
Tetanus toxoid	1
Tetanus-diphtheria (Td) toxoids	2
Typhoid fever, polysaccharide:	Vi – 1

Nomenclature: More Can Be Less

Nomenclature	Influenza or Poliovirus	Pneumo-coccal polysac-charide	Measles-Mumps-Rubella	Tetanus-diphtheria (Td) + typhoid Vi + anthrax	DTaP-HepB-IPV + Hib + MMR + Varicella + PNU7
Shots = Sticks = Injections = Jabs = 'Vaccinations' = Vaccine administrations	1	1	1	3	4 – 6
Diseases	1	1	3	4	9 – 11
Immunizations = Immune stimuli	3	23	3 or 24 (+liveness)	4 or 5	11 – 14 (+ liveness)
Immunogens = Antigens = Molecules	3	23	10 + 9 + ~5 = 24	2 + 1 + 2 = 5	1 + 1 + 2-5 + 1 + 15 + 2 + 10 + 9 + 5 + 69 + 8 = 126

- Wild-type infection involves more (~thousands) (and more complex) immune stimuli than vaccination.
- Vaccine selected to be milder and/or narrower array than circulating microbes

Limitations

- Focus on humoral vice cellular immunity.
- Analysis does not consider:
  - Immunodominant epitopes
  - MHC-limited responses to specific antigens
  - Conversion of naïve to memory cells
  - Immune system is not static
  - Immunogenetic risk factors

Veterinary Perspective

Relevant with regard to animal models of human immunology:

Common vaccines for livestock:

Duramune DA2PP+CvK/LCI (*Pfizer*): adenovirus type 1, adenovirus type 2, canine distemper virus, coronavirus, parainfluenza virus, parvovirus, Leptospira canicola, and Leptospira icterohaemorrhagiae.

CattleMaster 4+VL5 (*Pfizer*): bovine viral diarrhea (BVD), Campylobacter fetus, five species of Leptospira, parainfluenza-3 (PI-3) virus, respiratory syncytial virus, and rhinotracheitis virus.

IBR-BVD-PI3-Lepto-5 *8-Way* (*AgriLabs*): infectious bovine rhinotracheitis (IBR), BVD, PI-3, and five species of Leptospira.

ProSystem 2*1*4*3/B*P*E (*Intervet*): Bordetella bronchiseptica, Clostridium perfringens type C, Erysipelothrix rhusiopathiae, Escherichia coli, Pasteurella multocida (types A & D), rotavirus, and transmissible gastroenteritis (TGE).

Immunogenicity Issues

Comparable immunogenicity:

- Influenza + pneumococcal
- Hep A + Hep B
- Many childhood immunization regimens

  (see bibliography for examples of lack of interaction)

Immunogenicity idiosyncrasies of combining:

- DTaP – Hib – IPV – *et cetera*
- MMR + varicella (resolved by dose)
- Oral rotavirus + oral poliovirus
  - Some rotavirus strains, not others

Magnitude of Situation

Immunization Encounters,
U.S. Army, MedPROS database, Sep 02 to Oct 03

	Active	Guard	Reserve	Civilians	Row %	Cum %
1 A DAY	1,161,729	241,796	178,308	19,710	74.1%	74.1%
2 A DAY	173,682	67,484	37,751	1,293	13.0%	87.0%
3 A DAY	73,840	38,221	19,926	557	6.1%	93.1%
4 A DAY	31,425	27,111	15,529	376	3.4%	96.6%
5 A DAY	12,780	16,018	11,195	217	1.9%	98.4%
6 A DAY	4,591	7,220	7,754	139	0.9%	99.3%
7 A DAY	1,365	2,901	4,897	98	0.4%	99.8%
8 A DAY	580	981	2,020	36	0.2%	99.9%
9 A DAY	29	376	591	15	0.0%	100%
10 A DAY	2	47	82	1	0.0%	100%
11 A DAY	0	10	21	0	0.0%	100%

(excludes tuberculin skin tests) (not validated against paper records)

Magnitude of Situation

Immunization Encounters,
U.S. Air Force, AFCITA database, Sep 02 to Oct 03

	Active	Guard	Reserve	Row %	Cum %
1 A DAY	891,864	251,837	132,889	80.5%	80.5%
2 A DAY	132,863	44,334	24,834	12.7%	93.3%
3 A DAY	39,735	9,428	6,550	3.5%	96.8%
4 A DAY	35,953	5,293	3,582	2.8%	99.6%
5 A DAY	4,172	449	460	0.3%	99.9%
6 A DAY	632	93	77	0.1%	100%
7 A DAY	62	21	10	0.0%	100%
8 A DAY	14	7	9	0.0%	100%
9 A DAY	3	1	0	0.0%	100%
10 A DAY	2	1	1	0.0%	100%
11 A DAY	1	0	0	0.0%	100%

(e rculin skin tests)

Fort Detrick Multi-Dose, Multi-

White et al. Ann Intern Med 1974;81:594-600. www.anthrax.mil/media/pdf/Repeated.pdf

Participants: 99 men (mean: 40 y/o in 1958, 55 y/o in 1971).

Vaccines: 52 to 134 mL (mean: 97 ml) Skin tests: 6 to 93 (mean: 55)

Anthrax, botulism, brucellosis, EEE, influenza, plague, polio, psittacosis, Q fever, RVF, RMSF, smallpox, Td, tularemia, typhus, VEE, WEE, YF

Compared to 26 age- and gender-matched, unvaccinated control subjects

Design: Cohort study, occupational setting, 1944 to 1971

Findings: No clinical illness attributed to repeated immunization.

- Transient elevation in liver, kidney function WBC counts (absent in '74).
- No unusual diseases or unexplained symptoms.
- Mortality: Actuarial expectation = observed = 11 deaths.

"These data and the accompanying evaluation of an intensively immunized population provide evidence that no obvious adverse effects result from repeated immunization. … Thus, this group provides reassurance that schedules for routine immunization with a diversity of vaccines should not produce untoward effects merely because of frequency of inoculation."

IOM Findings re Children

Institute of Medicine. *Immunization Safety Review: Multiple Immunizations and Immune Dysfunction*. Washington, DC: National Academy of Sciences, Feb 2002. www.nap.edu/catalog/10306.html

- Favors rejection of causal relation with heterologous infection.
- Favors rejection of causal relation with type-1 diabetes.
- Inadequate evidence vis-à-vis allergic disease, particularly asthma.
- Does not recommend policy review vis-à-vis childhood immunization schedule.

But what about adults? Less risk, more risk, or just different?

Tolerability of multiple vaccinations in travel medicine

Börner, Mühlberger, & Jelinek. *J Travel Med*. 2003;10:112-6.

BACKGROUND: Travelers have time constraints, so multiple vaccination common. Data regarding tolerability sparse.

METHOD:

Prospective study of 1,183 healthy travelers before departure. Survey of side effects during, after vaccination.

RESULTS:

Frequency of side effects increases with # of simultaneous vaccines. Doubles—36.7%. Triples—40.3%, > 3—50.0%.

For >= 2 vaccinations, side effects less frequent than published.

Subjective rating: excellent tolerability of multiple vaccination.

CONCLUSION:

Multiple vaccines can be given at same time with limited subjective side effects.

Adverse reactions associated with simultaneous administration of multiple

- Falvo & Horowitz. *J Gen Intern Med*. 1994 May;9(5):255-60.
- OBJECTIVE: Determine frequency of local and systemic adverse reactions after simultaneous administration of multiple vaccines.
- DESIGN: Prospective survey given in clinic, returned 3 days later.
- PATIENTS: 984 patients over 1,205 visits. 64% returned survey.
- RESULTS: Local—58%. Any systemic complaint—39.5%.
  - Local reactions: 45% with 1 shot, 78% $\geq$ 3.
  - Systemic: 25% with 1 shot, 70% with $\geq$ 3.
  - # of vaccines did not influence duration or severity of reaction.
  - Age and gender did not influence frequency of reactions.
- CONCLUSION: Side effects for travel vaccination common. Increasing # of vaccines increases rates of local and systemic reactions. Reactions generally minor and not reason to withhold multiple vaccinations when needed.

ACIP General Recommendations on Immunization

- *MMWR* 2002;51(RR-2):1-35 ftp.cdc.gov/pub/Publications/mmwr/rr/rr5102.pdf
- Experimental evidence + extensive clinical experience strengthen scientific basis for administering vaccines simultaneously. Simultaneously administering all vaccines for which person is eligible is critical … Simultaneous administration critical when preparing for foreign travel and if uncertainty exists that person will return for further doses of vaccine.
- Inactivated + Inactivated: Simultaneous or any interval before/after
- Inactivated + Live: Simultaneous or any interval before or after
  - Except yellow-fever vaccine and parenteral cholera vaccine
- Live + Live: Simultaneous or $\geq$ 28 days apart
- Yellow fever vaccine any time after single-antigen measles vaccine
- Ty21a oral typhoid vaccine and parenteral live vaccines (i.e., MMR, varicella, yellow fever) simultaneously or any interval before or after

Bibliography

- Attached (incomplete) bibliography on simultaneous vaccinations:

  - Live + live: 13 articles
  - Live + inactivated: 33 articles
  - Inactivated + inactivated: 33 articles
  - General reviews: 4 articles
  - Other publications: 11 articles
    - Total 94

To Minimize Simultaneous

a. Spread ‘em out

b. Increase serologic screening

c. Increase acceptance of “reliable” childhood records

- Paper -- Electronic registries (States)

d. For the current force: “constructive credit” for basic training if records not available ?

*

- Presumption of immunity ?
- Disregard lack of records, unless in outbreak setting ?
- Tell computers not to alert over MMR or polio ?

e. Increase frequency of medical-readiness reviews (esp. RC)

f. Develop order-of-merit list ?

- Hep A, anthrax—high ? Polio, MMR—low ?

Initial Entry Training Regimen

- Meningococcal A/C/Y/W-135 (MGC)
- Measles-rubella (MR) or measles-mumps-rubella (MMR)
- Poliovirus inactivated (IPV)
- Tetanus-diphtheria (Td)
- Hepatitis A
- Hepatitis B

- Yellow fever (USN, USMC)
- Influenza (seasonal)
- Pneumococcal 23 (Camp Pendleton)
- Varicella (after screening, if susceptible)
- [*Adenovirus*] (anticipated 2007-08)

A proposal to spread 'em out …

Initial Entry Training ("basic training") (*imminent risks of contagion*):

- Meningococcal A/C/Y/W-135
- Measles-Mumps-Rubella (MMR, standard across Services) Live
- [Adenovirus—2007-08 ?] Live
- Influenza (seasonal)
- Varicella (if susceptible) Live
- Pneumococcal 23 (Camp Pendleton)

Advanced Individual Training (AIT) +/or 1st Duty Station (*generic travel risk*):

- Tetanus-diphtheria (Td)
- Hepatitis A
- Hepatitis B
- Poliovirus inactivated (IPV)
- Influenza (seasonal)
- Yellow fever (USN, USMC) Live

On the Horizon …

Don’t forget about desirable subunit vaccines on the horizon …

- Meningococcal group C conjugate
- Adult acellular pertussis vaccine
- Papilloma virus vaccine
- Others

Safety Research Efforts

Vaccine Analytic Unit (VAU) within Defense Medical Surveillance System (Army Medical Surveillance Activity), joint effort of CDC & DoD (w/ FDA)

1. Determine most common simultaneous combinations.
2. Are some combinations more problematic than others?
3. Possible studies: # of simultaneous exposures as continuous variable in triggering encounter for diagnoses within specified interval (eg, 60 d).
   a. total healthcare utilization (most sensitive; too nonspecific?)
   b. minor problems/discomfort (most common “sick call” ICD9 codes)
   c. autoimmune diseases (e.g., MS, GBS, DM type I, SLE)
   d. allergic diseases (e.g., asthma)
   e. other conditions to be determined
4. Possible Covariates: demographic factors, # of live vaccines, amount of aluminum, clinical history (eg, GBS), etc.
5. Search for risk factors that identify rare cases (“zebras”)

Safety Research Efforts

Other possible efforts:

- Armed Forces Institute of Pathology (AFIP):
  - Deaths 1998 to present, by cause of death and recency
- DoD Serum Repository:
  - Immunogenicity studies
    - Humoral >> cellular or innate immunity

Would you agree?

- There is no known ceiling of simultaneous immunizations that is “too many.”
- Simultaneous immunization bears considerable advantage in efficiently increasing the immunity of military personnel, returning them to duty with few medical visits.
- Published evidence and accumulated experience of tens of millions of simultaneous vaccinations over decades suggests that harm from simultaneous vaccinations *per se* (in contrast to same number of separate vaccinations) is either very rare or nonexistent [*or* ‘at most very rare’].
- Additional work is need to help identify risk factors that might predispose to rare problems.
- Because objective evidence is finite and because military databases offer unique opportunity to gather objective evidence in adults, these databases should be evaluated further.

- Would you agree ?